EARLY PREDICTORS OF CLINICALLY SIGNIFICANT BLEEDING IN ADULTS WITH DENGUE INFECTION

Supat Chamnanchanunt[1], Deena Kanagaraj[2], Vipa Thanachartwet[1], Varunee Desakorn[1] and Ponlapat Rojnuckarin[3]

[1]Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]Department of Community Medicine, Sri Ramachandra University, Chennai, Tamil Nadu, India; [3]Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract. Hemorrhage is an important complication in dengue infection, but early predictors of clinically significant bleeding are undefined. This study aimed to determine clinical factors on admission associated with Type I bleeding, defined as gastrointestinal bleed, hematuria and menorrhagia, among adult patients with dengue infection. We carried out a retrospective study among 277 patients aged >15 years with serologically-confirmed dengue infection admitted to the Hospital for Tropical Diseases, Bangkok, Thailand during 2006-2009. Female gender (p<0.001), vomiting (p=0.05), severe thrombocytopenia (platelet count < 25x 10^9/l; p=0.007), high absolute lymphocyte count (ALC >500; p=0.05) and high aspartate aminotransferase level (AST >200; p=0.02) were significantly associated with hemorrhage on univariate analysis. Multivariate analysis revealed variables associated with bleeding were female gender [odds ratio (OR) 14.5; 95% confidence interval (CI) 0.16-0.56, p<0.001], thrombocytopenia (OR 4.7; 95%CI 0.13-0.9, p=0.03) and ALC >500 (OR 5.7; 95%CI 1.17-4.99, p=0.02). These data identify patients at high risk for developing clinically significant bleeding with dengue infection.

Keywords: dengue, adult, clinical factor, clinical bleeding

INTRODUCTION

In Thailand, the number of dengue cases reported annually has increased over the years, with marked increases in the rates of adult infection (Kittigul *et al*, 2007; Chhina *et al*, 2009; Diaz-Quijano *et al*, 2010). Adult dengue cases have different clinical outcomes and mortality rates than pediatric cases (Wichmann *et al*, 2004). Case fatality rates with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are highest among the elderly (Lye *et al*, 2010). The case mortality rate may be up to 20% among patients with DHF and DSS, usually due to complications (Chaudhary *et al*, 2006; Kamil *et al*, 2006). Bleeding is the most common complication among adults (Rongrungruang and Leelarasamee, 2001; Ali *et al*, 2007).

Correspondence: Dr Supat Chamnanchanunt, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Bangkok 10400, Thailand.
Tel: +66 (0) 2643 5599; Fax: +66 (0) 2643 5598
E-mail: supat.cha@mahidol.ac.th

Thrombocytopenia (platelet count $<100 \times 10^9/l$) is associated with a greater risk of bleeding (Shivbalan *et al*, 2004; Makroo *et al*, 2007). Several studies have found other factors besides thrombocytopenia, related to bleeding (Srichaikul and Nimmannitya, 2000; Narayanan *et al*, 2002; Malavige *et al*, 2006a; Slichter, 2007). Many studies have evaluated clinical factors predictive of severe dengue infection; however, predictors of bleeding are unclear (Krishnamurti *et al*, 2001; Chaudhary *et al*, 2006; Chhina *et al*, 2009). Most studies have focused on pediatric patients. Data for adult dengue patients are sparse. Most studies used expensive, advanced laboratory methods, which are not suitable for general hospitals.

Our aims were to study the clinical characteristics that were different between adult dengue patients with and without clinically significant bleeding and to identify risk factors for the bleeding.

MATERIALS AND METHODS

We conducted a retrospective study of adult dengue patients admitted to the Hospital for Tropical Diseases, a 250 bed tertiary referral center in Bangkok, during 2006-2009. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (MUTM 2009-055-01). All eligible medical records of adults dengue cases of the Hospital for Tropical Diseases were reviewed. The sample size was determined based on a previous study which showed 26.6% of adult patients had bleeding complications (Wiwanitkit *et al*, 2004). The calculated sample size was 260 patients with laboratory confirmed dengue infection [95% confidence interval (CI)] with a 5% level of significance for bleeding.

Eligible cases were patients aged ≥15 years who had serologically confirmed dengue virus infection and met the WHO (1997) criteria for dengue infection (WHO SEARO and WHO WFRO, 1997). All patients were diagnosed by either a positive commercial NS1 antigen-based ELISA test (Standard Diagnostics, Suwon, Korea) or a dengue Immunoglobulin M (IgM) rapid test for dengue virus (Standard Diagnostics, Suwon, Korea). Patients with co-infections with other pathogens, with bleeding tendencies (hematological disease, liver disease, taking antiplatelet/anticoagulation medication) or with a history of bleeding were excluded from the study.

Enrolled patients were divided into 2 groups: 1) those with Type I bleeding and 2) those with Type II or Type III bleeding. Clinically significant bleeding was defined as Type I bleeding. Type I bleeding was defined by Chhina *et al* (2009) as gastrointestinal bleeding, hematuria, hemoptysis, or menorrhagia. Menorrhagia was defined as an abnormal menstruation in heaviness or extended duration. Type I bleeding was used as a study outcome, because it affected the physician's case management. Type II bleeding included epistaxis, gingival bleeding or other mucosal bleeding and Type III bleeding was bleeding in the skin or subconjuctiva.

The data were analyzed using SPSS for Windows version 18.0 (SPSS, Chicago, IL). Numerical variables were tested for normality using the Kolmogorov-Smirnov test. Variables with non-normal distribution were expressed as median and inter-quartile ranges (IQR) and the Mann-Whitney *U* test was used for comparisons between 2 groups. Categorical variables were expressed as frequencies and percentages, and then analyzed by the χ^2 test or Fisher's exact test, where appro-

Table 1
Baseline demographic data of 277 adult dengue patients with and without clinically significant bleeding.

Variables	Clinically significant bleeding (97)	No clinically significant bleeding (180)	*p*-value
	n (%)	*n* (%)	
Age	25.0 (21.0 - 31.5)[a]	22.0 (18.0 - 31.8)[a]	0.097
Gender			
Male	39 (40.2)	126 (70.0)	<0.001
Female	58 (59.8)	54 (30.0)	
Ethnicity (27)			
Thai	85 (88.5)	152 (84.4)	0.352
Non Thai[b]	11 (11.5)	28 (15.6)	
Residence (275)			
Bangkok	78 (81.3)	152 (84.9)	0.433
Outside Bangkok	18 (18.7)	27 (15.1)	
Workplace (269)			
School[c]	33 (36.3)	70 (39.3)	0.625
Non-school[d]	58 (63.7)	108 (60.7)	
Previous infection (83)	5 (17.2)	4 (7.4)	0.17
Underlying diseases (219)			
Respiratory illness	6 (7.5)	5 (3.6)	0.203
Hypertension	3 (3.8)	5 (3.6)	0.954
Metabolic disorder	2 (2.5)	5 (3.6)	0.663
Gastrointestinal illness	2 (2.5)	3 (2.2)	0.87
Other[e]	1 (1.3)	3 (2.2)	0.629

[a]Median (IQR); [b]Non Thai includes Myanmar, Vietnamese, Laos, Japanese and British
[c]Includes student and teacher; [d]Includes office worker, laborer, housewife, business person, unemployed, temple worker
[e]Includes rheumatoid arthritis, migraines, nephrotic syndrome and thalassemia

priate. Any variable with a *p*-value <0.2 on univariate analysis was considered significant and subsequently analyzed with multivariate logistic regression to determine independently associated risk factors for clinically significant bleeding in adult dengue infection. A *p*-value <0.05 was considered statistically significant.

RESULTS

Of the 277 adult dengue patients studied, 165 (59.6%) were male. The median age was 24 years old (IQR 19 - 31 years old). Most (85.9%) were ethnic Thais, Bangkok residents (83.6%), and had a non-school workplace (61.7%). Baseline demographic data, symptoms and signs on admission, laboratory findings and clinical outcomes for the studied patients are shown in Tables 1 to 4.

Ninety-seven cases (35.0%) had Type I bleeding during hospitalization. The top three kinds of Type I bleeding were hematuria (49.5 %), menorrhagia (36.1%) and melena (15.7%). The onset of bleeding

Table 2
Signs and symptoms of 277 adult dengue patients with and without clinically significant bleeding events.

Signs/symptoms	*n*[a]	Clinically significant bleeding (97)	No clinically significant bleeding (180)	*p*-value
		n (%)	*n* (%)	
Duration of fever (days)		5 (4-5)[b]	5 (4-5)[b]	0.355
Headache	185	61 (62.9)	124 (68.9)	0.312
Vomiting	141	57 (58.8)	84 (46.7)	0.05
Myalgia/Arthralgia	138	46 (47.4)	92 (51.5)	0.558
Fatigue	61	20 (20.6)	41 (22.8)	0.679
Abdominal pain	61	23 (23.7)	38 (21.1)	0.618
Diarrhea	57	22 (22.7)	35 (19.4)	0.525
Anorexia	36	11 (11.3)	25 (13.9)	0.547
Retro-orbital pain	2	2 (2.1)	0	0.122
Physical signs				
Temperature (°C)		38.0 (37.2-38.5)[b]	37.9 (37.2-38.5)[b]	0.614
Pulse rate (min)		86 (78-93)[b]	84 (78-88)[b]	0.13
Systolic blood pressure (mmHg)		108 (100-110)[b]	110 (100-120)[b]	0.491
Diastolic blood pressure (mmHg)		70 (60-70)[b]	70 (60-70)[b]	0.952
Pulse pressure (mmHg)		40 (30-40)[b]	40 (30-50)[b]	0.408
Height (cms)		163 (157-170)[b]	165 (159-171)[b]	0.878
Weight (kgs)		58.5 (49.0-67.7)[b]	55.2 (50.0-66.9)[b]	0.694
BMI[c] (*n*=197)				
Normal	113	38 (57.6)	75 (57.3)	0.65
Under weight	45	13 (19.7)	32 (24.4)	
Overweight	39	15 (22.7)	24 (18.3)	
Rash	88	36 (37.1)	52 (28.9)	0.161
Dehydration	83	29 (29.9)	54 (30.0)	0.986
Hepatomegaly	74	26 (26.8)	48 (26.7)	0.98
Tourniquet test (*n*=44)	25	6 (50.0)	19 (70.4)	0.221

[a]Number of presenting symptoms/signs and an individual patient might have more than one symptom and/or sign.
[b]Median (IQR); [c]BMI (body mass index); BMI <18.5 underweight; BMI 18.5 - 24.9 normal, BMI >25.0 overweight

ranged from the second to the eleventh day of hospitalization. Using the 1997 WHO case criteria for severity of dengue infection, 5 subjects (1.8%) had dengue fever, 80 subjects (28.9%) had grade I DHF, 189 subjects (68.2%) had grade II DHF, 3 subjects (1.1%) had DSS, and 3 subjects had grade III DHF. No subjects had grade IV DHF.

A comparison of adult dengue patients with and without Type I bleeding found gender significantly related to bleeding events ($p<0.001$) (Table 1). Other than fever, the three most common symptoms among those with and without

Table 3
Laboratory profiles of 277 adult dengue patients with and without clinically significant bleeding events[a].

Variables	Clinically significant bleeding (97)	No clinically significant bleeding (180)	*p*-value
	Median (IQR)	Median (IQR)	
Hemoglobin (g/dl)	14.2 (13.2-15.4)	14.8 (13.9-15.8)	0.373
Peripheral WBC	3,000 (2,200-4,375)	2,830 (2,200-4,075)	0.759
Neutrophils (%)	52.0 (35.0-68.5)	50.5 (36.2-64.3)	0.538
Absolute neutrophils	1,524 (1,050-2,099)	1,412 (990-2,044)	0.709
Lymphocytes (%)	30.0 (20.8-45.0)	34.0 (24.0-44.0)	0.369
Absolute lymphocytes	945 (494-1,587)	886 (610-1,446)	0.05
Atypical lymphocytes (%)	5 (0-10)	3 (0-9)	0.696
Absolute atypical lymphocytes	110 (0-388)	87 (0-277)	0.378
Platelet count (x 10^9/l)	51 (32-83)	76 (45-96)	0.007
AST (U/l)[b]	138 (79-257)	106 (60-175)	0.026
ALT (U/l)[b]	95 (50-166)	59 (60-137)	0.081
Globulin	3.3 (3.0-3.7)	3.4 (3.0-3.7)	0.925
Electrolytes			
Sodium (mmol/l)	135 (133-137)	135 (133-138)	0.791
Potassium (mmol/l)	3.5 (3.2-3.7)	3.7 (3.4-3.9)	0.782
Chloride (mmol/l)	100 (98-103)	100 (99-102)	0.998
HCO_3^- (mmol/l)	23.0 (21-25)	25.0 (23-26)	0.64
BUN (mg/dl)	9.0 (7-12)	10.0 (8-13)	0.99
Creatinine (mg/dl)	0.8 (0.7-1.0)	0.9 (0.8-1.1)	0.103
Serology			
NS1 Positive (56)	13 (68.4)	33 (89.2)	0.073
Dengue antibody (246)			
Only IgM positive	15 (16.5)	26 (17.4)	0.847
Both IgM and IgG positive	76 (83.4)	123 (82.6)	

[a]Median (IQR); [b]Both AST and ALT values use reference < 40 U/l
WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen

Type I bleeding were headache (62.9% and 68.9%), vomiting (58.8% and 46.7%), and myalgia/arthralgia (47.4% and 51.5%), respectively (Table 2). Vomiting was more common among bleeding cases (p=0.05). There were no statistically significanty differences in vital signs or physical findings between the patients with and without clinically significant bleeding, except for temperature and pulse rates, which were higher among the bleeding group (Table 2).

Adult dengue patients with Type I bleeding had significantly lower platelet counts (thrombocytopenia) and higher absolute lymphocyte counts than patients without clinically significant bleeding (p=0.007 and p=0.05, respectively) (Table 3).

Table 4
Clinical outcomes of 277 adult dengue patients with or without bleeding manifestations[a].

Outcomes	*n*	Clinically significant bleeding (97)	No clinically significant bleeding (180)	*p*-value
		n (%)	*n* (%)	
Duration of hospitalization (days)		3.85 (2.61-4.61)[a]	3.11 (2.61-4.61)[a]	0.075
Complications (*n*=267)				
Hepatitis	261	186 (98.4)	75 (96.1)	0.578
Hepatitis and plasma leakage	5	2 (1.1)	3 (3.8)	
Hepatitis and seizures	1	1 (0.5)	0	
Platelet transfusion	13	11 (11.3)	1 (1.1)	<0.001

[a] Median (IQR)

The bleeding group trended to have a longer period of hospitalization but this was not clinically significant (Table 4). Platelet transfusions were used more often in patients with clinically significant bleeding ($p<0.001$).

Univariate analysis ($p<0.2$) showed clinically significant bleeding was more frequent among patients presenting with five clinical parameters: female gender, vomiting, an absolute lymphocyte count >550/µl, severe thrombocytopenia (platelet count $<25 \times 10^9$/l) and hepatitis (AST >200 U/l).

Multivariate analysis showed three factors were independently related to clinically significant bleeding among adult dengue cases (Table 5): female gender [odds ratio (OR) 14.52; 95%CI 0.16 - 0.56, $p<0.001$], absolute lymphocyte count >550/µl (OR 5.78; 95%CI 1.17 - 4.99, $p=0.02$) and severe thrombocytopenia (OR 4.72; 95%CI 0.13 - 0.9, $p=0.03$).

DISCUSSION

Adult dengue infection carries a risk for bleeding complications (Guzmán *et al*, 2002; Garcia-Rivera and Rigau-Perez 2003; Wang *et al*, 2009). The complications can range from mild (petechiae) to severe (gastrointestinal hemorrhage) (Wiwanitkit *et al*, 2004).

Thirty-five percent of subjects in our study had Type I bleeding similar to other studies (Rongrungruang *et al*, 2001; Chhina *et al*, 2009). Seventy-three percent of subjects had bleeding in studies by Lee *et al* (2006) and Chandralekha *et al* (2008). However, only 15% had bleeding in a study by Makroo *et al* (2007). The reason for discrepancies in the incidence of bleeding is variations in the definition of bleeding.

Females had a greater tendency to develop Type I bleeding during hospitalization, similar to a study by Chandralekha *et al* (2008). This may be partially explained by menorrhagia. In the current study Type I bleeding was not more common among adult dengue patients with respiratory problems or hypertension. Some studies found asthma increased the risk for DHF (Lee *et al*, 2006; Figueiredo

Table 5
Univariate and multivariate analysis of clinical factors on admission for adult dengue patients with type I bleeding.

Predictors	Total subjects	Univariate analysis		*p*-value	Multivariate analysis		*p*-value
		OR	(95% CI)		OR	(95% CI)	
Gender: Female	277	22.32	0.172-0.483	<0.001	14.52	0.164-0.561	<0.001
Vomiting	277	3.667	0.373-1.012	0.05	1.93	0.352-1.194	0.16
Absolute lymphocyte count (ALC > 550)	277	6.187	1.163-3.576	0.01	5.78	1.179-4.999	0.02
Thrombocytopenia (Platelet count < $25x10^9$ cells/l)	300	4.274	0.188 -0.956	0.03	4.72	0.13-0.9	0.03
AST(AST > 200 U/l)	220	3.699	0.330-1.013	0.06			

et al, 2010; Lye *et al*, 2010). None of the patient in the present study had asthma.

Vomiting was significantly associated with Type I bleeding in this study on univariate but not on multivariate analysis. Vomiting is a predictor of severe dengue according to the 2009 WHO dengue classification (Kalayanarooj, 2011). Abdominal pain was not significantly more common among the Type I bleeding group. This may be because only a small number of patients were affected (Kalayanarooj, 2011). Wichmann *et al* (2004) found adult dengue cases with bleeding had higher rates of headache and myalgia.

Thrombocytopenia, with an evaluated absolute lymphocyte count and an evaluated AST level were all significantly associated with bleeding on multivariate analysis in our study. Nguyen *et al* (1997), Kuo *et al* (1992), Murgue *et al* (1999) and Wang *et al* (2009) found thrombocytopenia was associated with severity of disease. Other studies of adults with dengue fever found a platelet count < 50 x 10^9/l was associated with bleeding (Malavige *et al*, 2006b; Diaz-Quijano *et al*, 2008). In our study, platelet counts on admission ranged between 6 - 400 x 10^9/l; only 24 cases (8.6%) had a platelet count <25 x 10^9/l. Bleeding occurred when the platelet count was <25 x 10^9/l on admission. Physicians should monitor patients with a platelet count <25 x 10^9/l on admission carefully for signs of bleeding. A study by Thomas *et al* (2009) found severe thrombocytopenia (<10 x 10^9/l) was associated with critical bleeding less commonly than in our study since we only reported Type I bleeding. Another study reported hematemesis and melena were more common among patients with severe thrombocytopenia (Chairulfatah *et al*, 1995).

Our study found an association be-

tween a high absolute lymphocyte count and Type I bleeding. Elevated lymphocyte counts may be related to a high dengue viral load and bleeding episodes (Siqueira *et al,* 2004).

The duration of hospitalization among adult dengue patients with bleeding manifestations was longer in two previous studies than in our study (Lum *et al,* 2002; Malavige *et al,* 2006b).

The present study used only basic clinical and laboratory finding to predict clinically significant bleeding among adult dengue patients.

Our study had limitations inherent to retrospective studies. This study also only covered hospitalized adult dengue patients at a referral center specializing in tropical diseases; therefore these findings cannot be applied to other populations.

In conclusion, this study describes the clinical presentation, laboratory characteristics and disease severity of adult dengue cases with and without Type I bleeding. One-third of dengue subjects in this study had Type I bleeding. Female gender, severe thrombocytopenia (platelet count $<25 \times 10^9$/l) and an absolute lymphocyte count >500/µl were associated with Type I bleeding. A prospective study on this type of patient is warranted.

ACKNOWLEDGEMENTS

The authors are indebted to Varunee Desakorn for statistical analysis**.** The authors were supported in part by grants from the Faculty of Tropical Medicine, Mahidol University, Thailand.

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